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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/489,101 | 01/21/2000 | Ali O. Gure | L0461/7073(JRV) | 5361 |

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 19 |

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/489,101 | GURE ET AL. | |
| | Examiner | Art Unit | |
| | Thai-An N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,118,121,123,125,126 and 128-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1,2,7,16,50,52,63,65,70-72,78-80,85,88,98,102,109,115,118,121,125,126 and 128-135.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 7,16,50,52,63,65,70-72,78-80,85,88,98,102,109 and 115.

## DETAILED ACTION

Applicants' Amendment, filed 1/23/03, Paper No. 18, has been entered. Claim 1 has been amended.

Claims 1, 2, 7, 16, 50, 52, 63, 65, 70-72, 78-80, 85, 88, 98, 102, 109, 115, 118, 121, 125, 126 and 128-135 are pending. Claims 7, 16, 50, 52, 63, 65, 70-72, 78-80, 85, 88, 98, 102, 109 and 115 are withdrawn from consideration.

Claims 1, 2, 118, 121, 123, 125, 126 and 128-135 are under current examination.

Any rejection made of record in the prior Office action, mailed 10/17/02, Paper No. 17, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2, 118, 121, 123, 125, 126 and newly added claims 128-135 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, 1st paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at p. 1404 that,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The claims, as amended, are broadly drawn to methods of diagnosing cancer comprising: contacting a biological sample isolated from a subject with an agent that specifically binds to a nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an HLA molecule, wherein the nucleic acid molecule is selected from the group consisting of (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID Nos: 4, 11 and 12,wherein the hybridizing nucleic acid molecules code for a cancer associated antigen precursor, (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and (c) complements of (a) or (b), and determining the presence or level of interaction between the agent and nucleic acid molecule or the expression product as an indication that the subject has the cancer.

The specification teaches the isolation of eight gene products from the small cell lung cancer [SCLC] cell line [SEQ ID Nos: 3-10] and the isolation of 10 genes from the SCLC line SK-LC-13 [SEQ ID NOs: 3, 5, 6, 8, 11-17]. The specification provides teaching for the percentages of each of the clones [see Table 1a and 1b]. The specification teaches that Z1C2 [SEQ ID NO: 5] gene expression was analyzed by RT-PCR, and it was found that in normal tissues, ZIC2 mRNA was detectable in the brain and to a lesser extent testis, but it was not found in skin, kidney and small intestine. Further, the specification teaches that among tumor tissues, ZIC2 mRNA expression was found in varying degrees of expression in melanoma, colon cancer, breast cancer, heat and neck cancer, lunch cancer, transitional cancer, leiomyosarcoma and synovial sarcoma [see Table 2 and Example 3]. The specification teaches that SOX Group B family gene expression was analyzed by Northern blot. It was found that SOX2 [SEQ ID NO: 3] expression was detected in brain, testis, and prostate and at lower levels in the small intestine and colon of normal tissues, but SOX2 expression was not found in the heart, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, ovary and peripheral blood leukocytes. SOX1 [SEQ ID NO: 4], SOX3 [SEQ ID NO: 11] and SOX21 [SEQ ID NO: 12] mRNA was not detected in normal adult tissues. [See Example 4].

Applicants argue that the claims have been amended in several ways to overcome the enablement rejection. Firstly, that the claims now recite specifically the disorder that is diagnosed by the claimed methods, in particular, cancer.

Secondly, claims 1 and 2 have been amended to recite only the three nucleic acid sequences that are not expressed in any normal tissues as disclosed in the specification [SOX1, SOX3 and SOX21]. Thirdly, the other two nucleic acids, SOX2 and ZIC2 are now recited in individual claims and that these claims have excluded from them the particular normal tissues in which these two nucleic acids are not expressed. Applicants argue that accordingly, the claims as presently amended would not require undue experimentation because the claims are limited to detection of cancer, and are limited to application in tissues in which the specific genes are not normally expressed. Furthermore, Applicants argue that the methods that one of ordinary skill in the art would need to practice the claimed invention are well-known in the art, routinely practiced by one of ordinary skill in the art, and described in the specification to provide the skilled artisan with sufficient guidance to practice the claimed invention. As such, Applicants argue that the claims for methods of diagnosing cancer, as amended, would not require undue experimentation. See pp. 5-6 of the Response.

Applicants' arguments have been carefully considered, however, they are not found to be persuasive. Neither the specification nor the art teach the skilled artisan how to use the invention as broadly claimed. The specification and claims of the instant application assert that an agent that binds "specifically" to the nucleic acid molecule [SEQ ID Nos: 3, 4, 5, 11, 12] allows for the diagnosis of any cancer. The specification teaches generic methods for using the claimed sequences in

methods of diagnosis; however, the specification provides no specific guidance or teachings with regard to the level of interaction between the agent and the claimed nucleic acid molecule in order for detection of cancer. There is no indication in the specification of a threshold which would be indicative of any cancer, as broadly claimed. For example, if expression levels are significant in that the levels must reach a critical level for detection? Furthermore, it is noted that the mere presence of a particular transcript does not speak as to whether any protein is produced. The specification does not identify an open reading frame for this sequence, nor does it identify any encoded polypeptides. It is well-known in the art that many genes are potentially transcribed and expressed in cancerous, pre-cancerous and normal cells, as such one of skill in the art would have reasonable doubt that the particular sequences claimed would be useful as a cancer marker sequence.

It is well-known in the art that cancer diagnosis is a complicated and unpredictable field. Of the hundreds of types of cancer known, there are two to three times as many potential "marker" sequences published and studied. It is unlikely that the simple presence of a sequence, as those claimed, would be diagnostic for any type of cancer. Many so-called tumor markers in the art have been shown to be present in non-tumor tissues such that one of skill in the art would not have an expectation that any one sequence would be indicative of cancer. The claims as broadly written, read on any type of cancer, however, the specification only provides teachings with regard to the isolation of these genes from SCLC cell

lines. The specification fails to provide guidance or teachings with regard to what other cancers the claimed nucleic acid sequences would be expressed in, and while one could conduct additional experimentation to determine whether expression of any of the claimed sequences might be associated with certain types of cancers, the out come of such research cannot be predicted and such further experimentation and research are both unpredictable and undue.

With regard to Applicants' arguments that claims 128 and 132 have excluded from them the particular normal tissues in which these two nucleic acids are not expressed, this argument is not found to be persuasive. Firstly, the claims recite methods of diagnosing any type of cancer, however, the biological sample is isolated from tissues that are non-brain, non-testis, non-prostate, non-small intestine, and non-colon [claim 128] and non-brain, non-testis [claim 132]. It would not be possible to diagnose any type of cancer if certain tissue types are excluded, *e.g.,* prostate cancer.

It is reiterated that the teachings of the specification do not establish that one could actually detect expression of any of SEQ ID Nos: 3, 4, 5, 11 and 12 by hybridization such that one could diagnose any cancer, as broadly claimed. Rather, the specification teaches that some of SEQ ID Nos [SEQ ID NO: 3 and 5] are expressed in normal tissue types, that SOX1 [SEQ ID NO: 4], SOX3 [SEQ ID NO: 11] and SOX21 [SEQ ID NO: 12] are not expressed in normal tissues, but expressed in SCLC cell lines. As such, it is unpredictable as to whether one could successfully

use the claimed invention, and accordingly, it would require undue experimentation for the skilled artisan to use the claimed invention.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 118, 121, 123, 125, 126 and 128-135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 128 and 132 are vague. The claims recite that the agent "specifically" binds to a nucleic acid molecule. The term "specifically" is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, what degree/percentage/amount of specificity of binding would be required between the agent and the nucleic acid molecule to serve an indication that the subject has cancer? Claims 2, 118, 121, 123, 125 and 126 depend from claim 1; claims 129-131 depend from claim 128; claims 133-135 depend from claim 132.

*Conclusion*

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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